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OF

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By HERBERT FRENCH, M.D., F.R.C.P.

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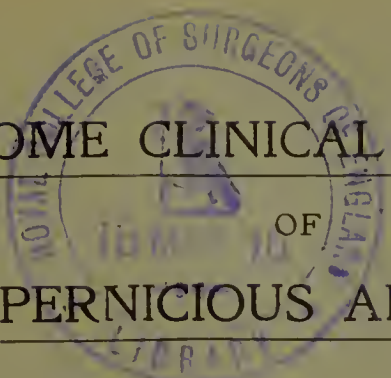

SOME CLINICAL ASPECTS OF PERNICIOUS ANÆMIA.

By HERBERT FRENCH, M.D., F.R.C.P.

The writer uses the term "pernicious anæmia" in a restricted sense. He does not include any case in which there is not at some time oligocythæmia with a high colour index and no leucocytosis, and should death occur, a definite Prussian blue reaction in the liver. Fifty-eight such cases passed through the wards of Guy's Hospital between 1890 and 1907. They illustrate some clinical points perhaps too little recognised.

1. THE TEMPERATURE.—There is constantly slight pyrexia. When the patient is ill enough to be admitted to hospital it is seldom that there is not a rise to 99° to 100° every evening. Pyrexia exceeding 101° is unusual, unless there is some intercurrent malady, such as tonsillitis or pneumonia. There is little tendency to subnormal temperatures in the morning, especially if the records are made only at 10 a.m. and 6 p.m.

Judging from other asthenic conditions, such as those associated with chronic heart disease for example, it would not have been surprising

if the temperature in severe pernicious anæmia had shown a tendency to be persistently subnormal. Judging from chronic sepsis on the other hand, one might have expected a moderate evening rise, and a considerable drop below normal in the morning. But neither of these types is at all like that of most cases of pernicious anæmia. The more the general condition improves the less does the tendency to evening pyrexia become.

2. Pigmentation of the buccal mucosa. Addison's disease and pernicious anæmia may present such similar symptoms that it is difficult to be sure which is present. It was thought that pigmentary deposits beneath the buccal mucosa would be decisive in favour of Addison's disease. This can no longer be maintained, for in the two following cases of pernicious anæmia, in which the diagnosis was confirmed by necropsy, the suprarenal glands were normal to the naked eye.

A shoemaker, aged 33, came under Dr. Hale White's care in 1904, and was in the hospital from Aug. 2 to Dec. 15. There was a long history of increasing weakness. He was not emaciated, though tall and spare. The lips were pale, but the skin, instead of being primrose or lemon yellow had an unhealthy sallow tint, and close inspection showed pigmentation, partly diffuse and partly in small localised dark brown freckle-like spots over the body, suggesting Addison's disease. This seemed to be confirmed by the presence of well-marked sepia-coloured pigmented areas and streaks within the mouth, particularly on the inner aspect of the cheeks, precisely as in Addison's disease. The difficulty was rendered greater, by variations in the colour index of the

blood, which was sometimes low and sometimes high. Dr. Hale White diagnosed pernicious anæmia, laying much more stress on the high colour indices than upon the low ones. Arsenical treatment was adopted, but without great relief, and later suprarenal extract, iron, and bone-marrow were tried. The patient went out a little better than when he came in, but was twice readmitted in 1905. He rallied again and lingered on till 1907, when he finally died. The necropsy showed that pernicious anæmia was the correct diagnosis and not Addison's disease. The blood-counts during life were as follows :—

Dat .	Red corpuscles per c.mm. (Thoma-Leitz).	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal (Haldane).	Colour index.	Leucocytes per c.mm.
1904					
Aug. 5	2,100,000	42	44	1·048	2400
Sept. 6	2,470,000	49	34	0·694	3125
Oct. 3	1,450,000	29	37	1·276	2656
,, 14	2,060,000	41	34	0·829	2188
,, 20	1,350,000	27	34	1·259	2810
Nov. 12	1,650,000	33	36	1·091	1800
Dec. 10	2,200,000	44	37	0·841	2000
1905					
Jan. 20	1,737,250	35	36	1·029	—
Feb. 3	1,350,000	27	27	1·000	1250
Dec. 2	1,750,000	35	45	1·286	1800

Both plantar reflexes were persistently extensor, though there was no ankle clonus, and no increase in knee-jerks.

A married woman, aged 33, who had been treated in St. Thomas's Hospital for pernicious anæmia, was admitted to Guy's Hospital in May, 1906. The case was a typical example of pernicious anæmia. The heart was a little dilated and there were generalised hæmic bruits and a *bruit de diable* in the neck. The liver

was 1½ in. below the ribs. The spleen was not felt. There were widespread pigmentation of the skin both in specks and spots and in bigger patches, and decided buccal pigmentation on the cheeks. The pigmentation was not known to have antedated arsenical treatment. The urine was high coloured and gave a well-marked urobilin band spectroscopically. The temperature often varied from 99° to 100°. The pulse-rate was 88 to 100 and the respiration-rate 20 to 24. Towards the end pleurisy set in and on Nov. 11 3 pints of fluid were withdrawn, followed on Nov. 25 by another 4 pints. She became collapsed, and died after the second aspiration.

Post mortem, inflammation of the alveolar sockets with looseness of all the teeth was found. The liver was large and pale and gave a good Prussian blue reaction. The kidneys were markedly anæmic and gave a slight Prussian blue reaction. The spleen was large, and pale red, and gave some degree of Prussian blue reaction. The marrow of the long bones was red. All the other structures and organs, except for pallor, looked natural. Microscopically the marrow showed well-marked megaloblastic change. The heart exhibited pigmentary degeneration, fatty change, and slight mononuclear infiltration. The iron granules in the liver-cells were chiefly at the periphery of the lobules. The spleen showed no fibrosis. The kidneys exhibited catarrhal changes in the tubules and also iron granules in the epithelial cells.

What *rôle* arsenic plays in the buccal pigmentation cannot be stated absolutely. In the Manchester epidemic of arsenical poisoning such pigmentation within the mouth was not

observed. Moreover, pigmentation of the skin may occur in pernicious anæmia even when no arsenic is given. Nevertheless, arsenic had been used in both the above cases, and therefore it cannot be said whether buccal pigmentation can occur in cases in which no arsenic has been used. The buccal pigmentation is precisely similar to that seen in Addison's disease.

3. The size of the spleen.—Although the general statement that the spleen is not enlarged may be true as a rule, nevertheless in some cases the spleen is large enough to be readily palpated. Clinically, out of 56 consecutive cases the spleen was felt with ease in 18. The degree of enlargement is comparable to that in typhoid fever; in the greater number the spleen extended below the costal margin for $\frac{1}{2}$ in. to 2 in., and in one to below the level of the umbilicus. Its weight varied from $3\frac{1}{2}$ to 26 oz. The fact that pernicious anæmia may cause definite enlargement of the spleen increases the number of conditions with which it may be confused.

(4) The nerve symptoms. — Dr. Gulland, of Edinburgh, has shown that nervous symptoms may not only be prominent in pernicious anæmia, but may also precede the recognition of the blood disease by weeks or months or even years. A patient attended at a special hospital for nerve diseases for symptoms which were regarded as those of locomotor ataxy for upwards of 2 years before the cord changes were recognised as being associated with pernicious anæmia. Various degenerations in the cord are often found post-mortem, particularly in the white matter, and when these are considerable the patient may

have presented symptoms suggestive of spastic paraplegia, ataxic paraplegia, locomotor ataxia, or simple ataxia, according to the parts of the cord most affected. Peripheral neuritis may also occur, but it is difficult to say to what extent this may be due to the arsenic given. It is less common, perhaps, for the complete signs and symptoms of any of the named diseases of the spinal cord to present themselves than for irregular nerve symptoms to appear, many of which are subjective, and, therefore, apt to be regarded as purely functional. In one case severe pains in the back, diagnosed as lumbago, had been a prominent symptom for years before the pernicious anæmia was recognised. The following have also been observed: headaches, gastric pains, numbness in the feet, with stumbling, paresis of the legs with ankle clonus, occasional absence of knee-jerks, paræsthesia of the thighs, with sensations in them described as their feeling "too hot inside and too cold out," delusional insanity, ideas of grandeur and symptoms precisely like those of general paralysis of the insane, persistent extensor plantar reflex on one side, flexor on the other, without ankle clonus.

(5) THE VARIABILITY IN THE COLOUR INDEX.—The final clinical criterion of pernicious anæmia is oligocythæmia with a high colour index and without leucocytosis. But the fact that the colour index proves to be low, or at least not high, when the blood is examined once only, or even more than once, does not exclude pernicious anæmia; for a series of blood-counts at intervals in the same case often show that there are periods when the colour index is less than 1 as well as other periods when it is greater than 1. Roughly speaking, the index tends to

be highest when the patient is most ill and anæmic, and to become lower as the condition improves. This is no absolute rule, however, for a high colour index may persist even when much improvement has occurred; on the other hand a low index is sometimes found when the patient is very ill. It is astonishing how quickly the index may vary: it may be high one week and low the next.

(6) THE INJUSTICE OF THE EPITHET "PERNICIOUS" IN SOME CASES.—The use of the term pernicious leads to an erroneous idea of the prognosis. It is true that hardly any patients with typical pernicious anæmia ever completely recover. It is also true that the end sometimes occurs within a month or a few months of what seems to be the beginning of the disease. On the other hand, the average duration of pernicious anæmia from the time of its recognition until death is in a fair number of cases to be measured in years. Moreover, the illness is not one of continuous downward progress like that of carcinoma of the stomach for example, for nothing in medicine perhaps is so striking as the way in which, even if the rally be only temporary, a patient who may seem to be *in extremis* from pernicious anæmia, with his red corpuscles under 20 per cent. of normal, may recuperate, not only once, but several times. Out of 40 cases the writer has found that the interval between recognition of the disease and death in 15 was more than a year, and that in 8 of these the patient survived the diagnosis from 2 to 10 years. Lymphatic leukæmia is far more pernicious a complaint than is pernicious anæmia.

(7) THE DIFFICULTY IN ACCURATELY DATING THE BEGINNING OF THE ILLNESS.—

The diagnosis is chiefly by means of blood-counts; but in the majority of cases this by no means coincides even with an early stage much less with the beginning. Symptoms are present for years before the anæmia becomes pronounced. In most cases the onset is insidious and in a number the early symptoms are attributed to some different malady—typhoid fever, for example; English cholera when diarrhœa is prominent; a chronic nerve disease; functional disorder of the stomach, and so on.

The writer suggests that pernicious anæmia may be but a late phase of a more general disease which is at present unnamed. Not many years ago it was impossible to diagnose early phthisis, and consumption was regarded as essentially fatal because it was only recognised when it had already passed beyond the stage when it was curable. The end, in cases of phthisis, may be very rapid by galloping consumption, comparable to acute cases of pernicious anæmia; or the end may be gradual with periods of recovery and relapse extending over months or years comparable to the ordinary course of pernicious anæmia. On the other hand, if recognised at a stage at which our grandfathers would have denied the existence of phthisis, consumption may be cured. Perhaps pernicious anæmia, as we know it, is but a late stage of a much commoner malady in which recovery spontaneously occurs in many cases, breaking out into an acute phase in others, running a subacute or chronic up-and-down course in yet others. We are now able to recognise phthisis early, by bacteriological and other means. It is to be hoped similar early recognition of pernicious anæmia will become possible.